Agomelatine for depression in schizophrenia: A case-series

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Abstract: OBJECTIVES: Agomelatine, a melatonin (MT1/MT2) receptor agonist and 5-HT2C receptor antagonist, is a new antidepressant and a potential therapeutic option for major depressive episodes and negative symptoms in persons with schizophrenia. We investigated such treatment outcomes with respect to antidepressant efficacy, safety, and tolerability. METHODS: We report a consecutive case series of seven patients with schizophrenia and comorbid major depressive symptoms who received agomelatine for a period of at least six weeks in addition to stable doses of antipsychotic agents. General psychopathology, positive, negative and depressive symptoms were assessed with standardized interviews. Relevant blood parameters were assessed. RESULTS: Depressive symptoms improved significantly. Positive symptoms remained stable, while negative symptoms and global psychopathology improved significantly. Agomelatine was well tolerated in most patients. CONCLUSIONS: Our findings provide initial evidence that agomelatine is safe and efficacious in treating depressive symptoms in patients with schizophrenia. Furthermore, agomelatine seems to be effective for the treatment of negative symptoms. Randomized controlled trials are necessary to confirm these first observations.

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RESEARCH ARTICLE

Key Words: agomelatine, schizophrenia, antidepressant, antipsychotic, depression

Agomelatine for Depression in Schizophrenia: A Case-Series

By Jochen Mutschler, Nicolas Rüsch, Herdis Schönfelder, Uwe Herwig, Annette B. Brühl, Martin Grosshans, Wulf Rössler, Heike Russmann

ABSTRACT ~ ***Objective:*** *Agomelatine, a melatonin (MT1/MT2) receptor agonist and 5-HT2C receptor antagonist, is a new antidepressant and a potential therapeutic option for major depressive episodes and negative symptoms in persons with schizophrenia. We investigated such treatment outcomes with respect to antidepressant efficacy, safety, and tolerability.* ***Methods:*** *We report a consecutive case series of seven patients with schizophrenia and comorbid major depressive symptoms who received agomelatine for a period of at least six weeks in addition to stable doses of antipsychotic agents. General psychopathology, positive, negative and depressive symptoms were assessed with standardized interviews. Relevant blood parameters were assessed.* ***Results:*** *Depressive symptoms improved significantly. Positive symptoms remained stable, while negative symptoms and global psychopathology improved significantly. Agomelatine was well tolerated in most patients.* ***Conclusions:*** *Our findings provide initial evidence that agomelatine is safe and efficacious in treating depressive symptoms in patients with schizophrenia. Furthermore, agomelatine seems to be effective for the treatment of negative symptoms. Randomized controlled trials are necessary to confirm these first observations.* Psychopharmacology Bulletin. *2012;45(1):35–43.*

Introduction

Depressive and negative symptoms are common in people with schizophrenia[1–3] and have been associated with poor quality of life[4] and with overall worse outcomes.[5,6] Depressive symptoms can occur during a comorbid major depressive episode. They may also be secondary, e.g. due to adverse effects of antipsychotics[7] or a psychological reaction to stress or other comorbid disorders (e.g. substance use disorders). Depressive symptoms are common throughout various phases of

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the illness in patients with psychotic disorders and do not respond well to current antipsychotic treatment.[1] Different antidepressant agents, and some atypical antipsychotics, have been successfully used in the treatment of depressive symptoms in patients with schizophrenia.[8–11] However, to our knowledge, there is only one case report on the use of agomelatine in the treatment of depressive symptoms in schizophrenia published so far.[12]

The mode of action of this antidepressant agent is very promising: Antagonism at the serotonin subtype 2C (5-HT2C) receptor significantly improves incentive motivation and therefore has been suggested as a therapeutic approach to ameliorate the lack of motivation in patients with schizophrenia and depressive disorders.[13–15] Agonism on the melatonin (MT1/MT2) receptors has clinically significant antidepressant and anxiolytic properties.[12,16–19] Additionally, agomelatine has chronobiotic effects, caused by the synergy between the melatonin-based and monoamine-based psychotropic effects.[18,20] Therefore, we examined safety and efficacy of agomelatine in a case series of patients with schizophrenia that developed depressive symptoms under continuous antipsychotic treatment.

METHODS

Patients and Therapy

We report on seven patients (three male, four female) that fulfilled the diagnostic criteria for psychotic lifetime diagnoses and current major depressive episodes according to the International Classification of Diseases, 10th Revision (ICD-10), and received agomelatine as antidepressant treatment. For patient details see Table 1.

The patients were treated in the outpatient clinic of the Psychiatric University Hospital Zürich. On average, first onset of psychosis occurred at 8.71 ± 2.14 (mean ± SD) years ago, with 2.43 (±1.62) psychotic episodes and 2.71 (±1.80) hospitalizations. First depressive symptoms occurred 3.07 (±2.05) years ago, the patients had suffered 2.14 (±1.21) previous major depressive episodes before the current index episode. At treatment initiation, positive symptoms rated by the Positive and Negative Syndrome Scale (PANSS) were 17 (±8.76), respectively 35.14 (±9.86).

Design and Evaluations

We present data of a retrospective case study of persons with schizophrenia and comorbid major depression who received agomelatine as

TABLE 1

Patients Characteristics: Sociodemographic Data, Clinical Characteristics and Psychiatric Medication

Patient	Age (years)	Gender	Currently employed	Living in partnership	Psychiatric diagnoses (ICD-10), except affective disorders	Affective disorder (ICD-10)	Number of previous psychiatric inpatient treatments	Current psychiatric medication	Agomelatine dose (mg/day)
A	31	female	no	yes	F20.0	F33.1	1	Risperidone (3 mg/day)	25
B	49	male	no	yes	F20.0 F63.8 (Chronic lumbar spondylogenic pain syndrome)	F33.2	3	Paliperidone (6 mg/day) Clozapine (50 mg/day) Venlafaxine (150 mg/day) Pregabaline (300 mg/day) Valproate (1500/day)	25
C	45	female	no	no	F20.0	F33.1	4	Risperidone (4 mg/day)	25
D	52	female	no	no	F20.0	F32.1	5	Paliperidone (6 mg/day) Biperidene 4 mg/day	25

(*continued*)

TABLE 1 (*CONTINUED*)

PATIENT	AGE (YEARS)	GENDER	CURRENTLY EMPLOYED	LIVING IN PARTNERSHIP	PSYCHIATRIC DIAGNOSES (ICD-10), EXCEPT AFFECTIVE DISORDERS	AFFECTIVE DISORDER (ICD-10)	NUMBER OF PREVIOUS PSYCHIATRIC INPATIENT TREATMENTS	CURRENT PSYCHIATRIC MEDICATION	AGOMELATINE DOSE (mg/DAY)
E	40	male	no	no	F20.0 F12.1	F32.1	1	Olanzapine (10 mg/day) Escitalopram (10 mg/day)	50
F	48	female	no	yes	F20.0 F10.1 F40.1	F32.1	1	Amisulpride (400 mg/day) Lamotrigine (250 mg/day) Risperidone (6 mg/day)	50
G	23	male	no	no	F20.0	F33.1	2	Clozapine (50 mg/day) Escitalopram (10 mg/day)	50
Mean	41.14						2.43		35.71
SD	10.61						1.62		13.36

antidepressant treatment in our outpatient centre between January and July 2011. According to the local ethics committee it is permitted to retrospectively analyse anonymized clinical data for research purposes.

Demographics, laboratory data (serum levels of gamma-glutamyltransferase (GGT) and liver enzymes), clinical and psychiatric history, and psychopharmacological treatment data were assessed retrospectively using electronic charts. Primary endpoint of the study was the difference of depressive symptoms as measured by the 21-item Hamilton scale for depression (HAMD)[21] and the Calgary depression scale for schizophrenia (CDSS)[22] across four time points (interval of 2 weeks). Secondary endpoints were the difference of anxiety symptoms, positive and negative symptoms over time as assessed with the PANSS and the Hamilton Scale of anxiety symptoms (HAMA). Regular clinical assessments included the German versions of the PANSS, Scale for the Assessment of Negative Symptoms (SANS), CDSS, HAMD and HAMA, starting before the first dose of agomelatine. Exploratory outcome measures were treatment adherence and safety and tolerability of the treatment.

Statistics

Descriptive statistics are given when appropriate (mean ± SD). Mean comparisons were performed by using one-way repeated-measures ANOVAs (with the factor time to compare the mean scores over four different time points). Results were corrected for multiple comparisons using Bonferroni correction. Results were considered significant at $p < 0.05$. Statistical analyses were performed using SPSS for Windows version 18.0 statistical software (SPSS Inc, Chicago, Illinois).

RESULTS

Characteristics of the Patients

Three patients were treated with more than one antidepressant drug. In these cases, agomelatine was used as a second antidepressant because of insufficient response to the first one. Two patients were additionally treated with escitaloprame (10 mg/day), and one was treated with venlafaxine (150 mg/day). With respect to antipsychotic treatments, three patients were treated with risperidone, two with paliperidone, one with amisulpride, and two received clozapine. Five patients were treated with one antipsychotic drug, while two received two antipsychotics. Furthermore, three patients were treated with additional psychotropic medications, one patient with an anticholinergic medication, and two

with antiepileptics. Except agomelatine, medications remained stable during observation time. Agomelatine was administered at a dose between 25 or 50 mg/day, dependent on the clinical response.

Outcome

The scores in the different scales and subscales are presented in Figure 1.

Through agomelatine treatment at a mean dosage of 35.71 (SD = 13.36) mg/d, we found overall significant improvement of depressive and negative symptoms (CDSS: $F = 7.89$; $p < 0.001$, mirrored by a response (50%-reduction of symptoms) in three patients, and a complete remission of the depressive syndrome in 1 patient, respectively. Furthermore, HAMD21 scores (HAMD21: $F = 11.55$; $p < 0.001$) and also anxiety symptoms (HAMA: $F = 3.26$; $p < 0.05$) decreased. In one patient treatment with agomelatine had to be stopped because of side-effects (see below).

In parallel with improvement of depressive symptoms, we observed an improvement of the psychotic negative syndrome (PANSS negative: $F = 8.05$; $p < 0.001$; SANS: $F = 8.6$; $p < 0.001$), associated with a decrease of global psychotic symptoms (PANSS GP: $F = 6.15$; $p < 0.05$; PANSS PSY: $F = 9.41$; $p < 0.001$). Psychotic positive symptoms remained unchanged over time (PANSS P: $F = 2.06$; $p = 0.13$). Preexisting psychotropic comedication remained unchanged during the observation period.

Safety and Adverse Events

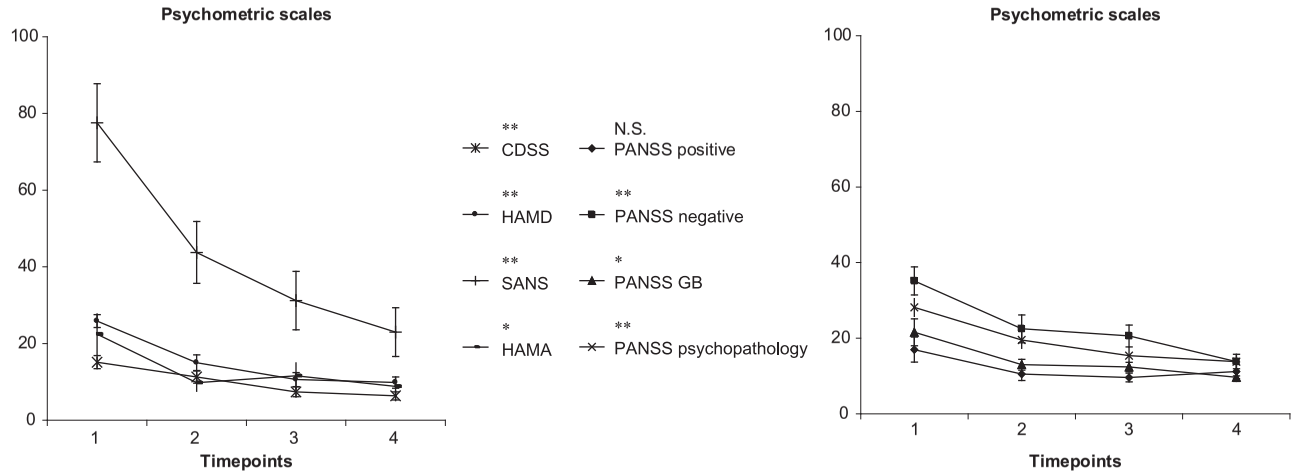
The electronic patient records did not show any serious adverse events (e.g. hepatitis). However, one patient discontinued the treatment with agomelatine immediately because of intolerable side-effects (namely: headache, diarrhea, vertigo and nausea). In general we observed common side-effects such as headache (n = 2), dizziness (n = 1), diarrhea (n = 1), insomnia (n = 2), and sweating (n = 1). However, these side-effects disappeared completely within the first weeks of the treatment if continued. We observed a marginal and transitional increase of liver enzymes in one patient (n = 1).

DISCUSSION

This case series on agomelatine revealed significant improvement over time in depressive and anxiety symptoms among patients with schizophrenia and depressive symptoms. General psychopathology, particularly negative symptoms also improved, whereas positive psychotic

FIGURE 1

The Figure Shows the Course of the Clinical Scores Over Four Different Time Points. Results are Indicated as Mean Values and Standard Error (SE)



CDSS: Calgary Depression Scale for Schizophrenia; HAMD: Hamilton Depression Scale; SANS: Scale for Assessment of Negative Symptoms; HAMA: Hamilton Scale of Anxiety Symptoms; PANSS: Positive and Negative Syndrome Scale.

*$p < 0.05$; **$p < 0.001$ (One-way ANOVA).

symptoms remained consistently stable. According to current lines of evidence the compound has been studied primary as antidepressant drug, moreover, agomelatine has anxiolytic and chronobiotic effects.[18] However, in the context of schizophrenia and depressive symptoms the mode of action of agomelatine is of special interest. Patients suffering from schizophrenia and comorbid major depression are difficult to treat, not least, because additionally these patients often suffer from negative symptoms. The antagonism of the 5HT2C receptors and consecutive increase of dopamine and norepinephrine concentrations in the prefrontal cortex could be helpful concerning negative symptoms and anhedonia, often associated with major depression in schizophrenia.[23] In our study we demonstrated effectiveness, good tolerability and safety of agomelatine in the treatment of depressive symptoms in patients suffering from schizophrenia. Moreover, negative symptoms improved in most patients. While one patient discontinued the treatment with agomelatine because of side effects, all other patients tolerated the medication well.

Our retrospective evaluation has several limitations and allows only cautious interpretation of efficacy and safety features: Because the number of cases is small, more or different side-effects could occur in a larger sample. Although co-medications of our patients during the observational period remained constant, we cannot exclude interactions that influenced the outcome.

Nevertheless, a strength of this case series is the naturalistic outpatient setting providing evidence that a successful therapy of schizophrenic patients with concomitant negative symptoms and major depressive episodes is feasible. Uncontrolled case observations are useful as initial evidence about a drug's efficacy and tolerability. In addition to pharmacotherapy, it is also important to keep in mind that a combination of psychosocial treatments, psychotherapy, group therapies and contingency management therapies are efficient and necessary for a successful therapy. Randomized-controlled clinical trials are warranted to confirm our preliminary results. ✤

Disclosure

The authors declare: There are no conflicts of interest.

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